April, 1969

Vol 96 No 4

How close is an "improved" cigarette?

- New theories involve CRNA viruses and cell fermentation (pages 17-21)
- Methods have been devised to remove almost anything from smoke including elusive CO and NO (pages 22-26)
- What about artificial tobacco? (*Tobacco Reporter* smoked a paper cigarette in California — see pages 28-32)

Dr. Carl Baker, chairman of the Tobacco Work Group, which is a sub-committee of the Presidential Lung Cancer Task Force, has compared the task of coming up with a "health improved" cigarette to that of getting a man on the moon. But nowhere near as much money is available for the cigarette problem, although in February the work group finally received its $1.4 million appropriation.

Updating figures from the February, 1968, *Tobacco Reporter,* it appears that last year some $15.4 million was spent in the U. S. for research on smoking and health. Much of this was spent to help identify and produce such a cigarette. More than half of the funds are coming from the tobacco industry. (See page 20.)

But the major problem remains the same. As Luther Terry explained in 1964, when he was Surgeon General, "It is difficult to design a method of removing something if you don't know what it is." Additionally, there is still the possibility that the statistical correlation between cigarette smoking and lung cancer, along with several other diseases, is a genetically or environmentally caused accident.

Research efforts have shaped up like this. When statistical studies began to indicate a correlation between cigarette smoking and lung cancer, researchers rushed out to produce lung cancer in animals with cigarette smoke. The theory being that by removing various ingredients from the smoke, the cause could be identified.

On Mouse Painting

The problem was that they didn't seem to be able to give lung cancer to animals through cigarette smoke inhalation. So other routes

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were tried. Initially researchers found that concentrated particulate matter, when painted on the backs of mice, could produce cancers. Early excitement over the discovery may have been enhanced by the fact that on first tests some 40 per cent of the mice developed these tumors. Later tests showed the rate to be closer to 4 or 5 per cent.

Dr. Robert Hockett, associate director of Council for Tobacco Research U.S.A. (CTR), has often referred to mouseback painting as use of the *"wrong material"* (concentrated particulate — sometimes erroneously called "tar" — differs greatly in content from fresh tobacco smoke), *"on the wrong tissue"* (lung tissue, which is covered with a mucus layer, differs greatly from mouse back skin), *"in the wrong doses, on the wrong animal"* (mouse is quite different from man).

A basic problem with particulate painting is that the material is highly concentrated. Scientists recognize that there are a number of carcinogens (cancer-causing materials such as 3,4 benzpyrene) in cigarette smoke but the doses in smoke are far below what would be needed to produce cancer. In fact one researcher reports that a man would have to smoke 100,000 cigarettes a day to reach a cancer-causing dose level with the carcinogens identified in cigarette smoke. Nonetheless when such ingredients are highly concentrated and painted on sensitive mouse skin — generally cancer-prone mice are used — obviously they will produce cancer.

Because of the low dosage of these carcinogens in cigarette smoke the direct contact theory has more or less gone "by the board." Today most researchers feel that if cigarette smoking causes cancer the mechanism is far more complicated.

Theories About "Tar"

Among those researchers most concerned with particulate matter, favorite theories are "co-carcinogens," and "combination with irritants." The "co-carcinogen theory" holds that maybe certain ingredients in cigarette smoke such as phenols act to enhance cancer-causing abilities of such carcinogens as 3,4 benzpyrene or polonium 210. The "combination with irritants" theory holds that perhaps irritants such as hydrogen cyanide or acrolein in the gas phase — which have proved ciliastatic in animal studies — retard cilia, thus reducing lung clearance and allowing the carcinogens in cigarette smoke to build in the lung, enhancing their ability to react with the lung surface. Although tobacco particulate is a relatively weak carcinogen, mousepaintings have shown it to be an effective cancer promoter.

Both of these remain theories, as they have not been proved out with laboratory animals, nor, obviously, with humans. Results of tests with animals to demonstrate these theories might indicate a need to look elsewhere for an answer.

New Theories — Viruses

In recent months several new theories have emerged. One of the most interesting resulted from analyses of tumors identified by Dr. Cecile Leuchtenberger in her on-going mouse inhalation experiments in Switzerland. (See *Tobacco Reporter,* February, 1969.) Dr. Leuchtenberger claims to have identified certain glandular cancers — adenocarcinoma — in mice smoking pure gas phase of cigarette smoke, and even more such tumors in mice smoking fresh smoke. The tumors appeared both in lungs of the mice and in the liver but did not appear similar to the squamous cell carcinoma that appears statistically linked with lung cancer in the human male.

In inspecting some of these tumors one cancer and virus specialist at National Cancer Institute noted that resulting liver tumors in the cigarette and gas phase smoking mice seemed to be of a type caused by a C variety RNA virus. Does this mean that something in the cigarette smoke, and more particularly in the gas phase, preconditions the mouse to be susceptible to certain virsuses? Which gasses might be taken into the system of the mouse to set off such a reaction?

The discovery really raises more questions than it answers. In the first place, some viruses have been demonstrated to produce cancers in rodents; this has not been demonstrated with humans yet, although a breakthrough with a leukemia virus may be forthcoming this year. It also makes predisposition to latent viruses in laboratory mice a significant factor that must be controlled in laboratory inhalation experiments.

But the greatest question raised is *how* cigarette smoke might act with viruses to produce cancers and which ingredients might be involved. Dr. Loren J. Humphrey, formerly an associate professor of cell biology, did some work along these lines with the University of Kentucky Smoking and Health Research Project.

Dr. Humphrey's work dealt largely with a model using methylcholanthrene (not in cigarette smoke) as a carcinogen in a study that was to prototype one on the role of tobacco condensate. Based on results with the methylcholanthrene model, which suggested passage of a virus, Dr. Humphrey had plans to prepare an extract from cigarette smoke condensate-induced sarcomas and innoculate this into mice to determine its carcinogenic potency.

If it develops that cigarette smoke in some way triggers cancer-producing viruses, pathways may be laid toward removing the effect, and in fact toward understanding and possibly preventing cancers other than those of the lung. It is not surprising that CTR is now channeling additional funds in this direction, and has several projects underway.

One research area of special interest is "interferons" — an anti-virus substance produced by animals for protection. Apparently these cannot be transferred from one animal to another but they may be artificially induced in animals. Research projects are being set up to explore "interferons" that may affect viruses such as C type RNA.

Meanwhile, the Leuchtenberger team has plans to visit the United States for at least a month this summer to work with Dr. Robert Heubner, director of the virus division of National Cancer Institute. It is logical to assume that much future work of the Leuchtenbergers may be directed toward study of viruses and their role and induction with tobacco smoke and its various components.

A number of inhalation studies have already been performed with cigarette smoke and viruses. These include work of Harris-Negroni in Britain and some earlier work of the Leuchtenbergers. These, however, involved largely influenza virus, which may not promise the significance in carcinogenesis of certain latent mouse viruses such as the C type RNA. Although Harris-Negroni did observe increased tumors with combined influenza virus and cigarette smoke — in fact they managed to produce the tumors with the influenza virus alone — there has been some difficulty in reproducing the Harris-Negroni results.

If the virus theory proves true, the need for experimental mice with a controlled level of viruses becomes evident. Interestingly Dr. Hockett reports that CTR now feels such strains of mice are possible, and will add meaning to future experiments.

The Oxygen Theory

Another theory is currently being expanded by Dr. Dean Burk, a cell physiologist at NCI. Dr. Burk is a strong proponent of carcinogenesis theories of Dr. Otto Warburg of Max Plank Institute in Germany. Dr. Warburg holds that all tumors ferment and that advanced ones obtain most of their energy from fermentation rather than oxidation. He charges that such an effect can be caused by anything that blocks normal oxydation pathways such as injury or respi-

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Who's paying for the

Last year more than $25 million was spent on smoking and health research around the world, largely in the U. S., Britain, Germany and Switzerland. Yet the major questions are still unanswered. If cigarette smoking causes disease, what are the mechanisms?

The U. S. Government has talked about — but apparently discarded — a five-year $50 million crash project toward finding an "improved" cigarette. Yet the government in February did come through with $1.4 million for the new Tobacco Work Group — the cigarette sub-committee of the Presidential Lung Cancer Task Force.

The Work Group, which includes research specialists from the tobacco industry as well as private and government researchers, met on March 30 to map out how this money will be spent. They must spend it by June.

Indications are that most of it will go into contracts for bio-assay development, and much of the work will be done at the Enviromental Health Center in North Carolina, which was recently made a separate Institute in the National Institutes of Health. Interestingly, Dr. Paul Kotin, who heads the Environmental Institute, was the brain behind the $50 million crash project idea. And although $1.4 million is far from $50 million, there are indications that the annual appropriation may be increased as needs of the Work Group expand.

Last year a minimum of $15.4 million was spent in the U. S. on smoking and health research. This was up considerably from the minimum figure of $12.45 million *Tobacco Reporter* computed for fiscal 1967 in February, 1968.

The tobacco industry still appears to be the biggest spender in the area of pure smoking and health research. Unrestricted funds dished out by Council for Tobacco Research-U.S.A. — sponsored by cigarette manufacturers — increased to $1.9 million last year. And American Medical Association distributed another $2 million of industry money through the Educational and Research Foundation.

At the same time, cigarette manufacturers appear to be pouring larger amounts of money into research efforts — many that relate directly to the smoking and health question. Press releases of the Tobacco Institute have described internal research as representing "at least as much" investment annually as funds committeed to the CTR and AMA funds.

In addition to maintaining large research staffs and facilities of their own, most of the tobacco companies also do outside research on contract — such as Liggett & Myers' sponsorship of studies at Arthur D. Little Inc. — as well as making private grants to institutions and hospitals for work in this area. While a flood of patents from industry suppliers such as paper, equipment, charcoal and filter tow suppliers would indicate accelerated investment from this segment as well.

INDUSTRY — $8.8 million

CTR	$1.9 million
AMA-ERF	2.0 million
Manufacturers	3.9 million
Suppliers	1.0 million

The problem with estimating funds spent for smoking and health research is that much research indirectly touches on smoking and health. In the case of cigarette companies, for example, it is difficult to identify chemical research that is directly health related, from similar work on taste or product quality. In computing government figures, it appears that much research is epidemiological — done through questionnaires. What if one question on a 25-question form filled out by emphysema victims relates to smoking? Should cost of this study be included?

Government - HEW

Department of Health, Education and Welfare started to solve this problem by coming up with two figures for

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ratory poisons, which might include several ingredients in cigarette smoke such as hydrogen cyanide or carbon monoxide.

Dr. Burk and his co-workers prepared an abstract of some on-going research that was published last month. Dr. Burk's current work shows apparent disruption of cell respiration and interference with respiratory enzymes from both cigarette and cigar smoke. By measuring increases in fermentation, the degree of interference with respiration can be measured. Under these circumstances proper quantities of whole smoke will destroy the cell by abrupt and severe deprivation of energy. Smaller quantities of smoke will measurably disrupt this respiration, but will allow the cell to survive apparently seeking to replace the lost energy source through fermentation. In this replacement they begin to resemble maligant cells.

Dr. Burk's work is still underway, but initial results indicate that much of the activity — although perhaps less than half — resides exclusively in the gas phase. Interestingly, carbon monoxide alone seems to have little effect on the cells — thus might be exonerated. The rest of the activity appears in particulate phase, but effects seem concentrated in the more volatile portion of particulate that includes such middle molecular weight ingredients as toluene, benzene and phenols.

Dr. Burk found results consistent no matter what type of cell was used — bone marrow, lung tissue or kidney tissue. Along these lines it is interesting to note that Dr. Camille Izard in a French study published in 1967, got similar results by subjecting algae to both cigarette smoke, gas phase and acrolein from the gas phase. He also observed cell mutations in algae exposed to acrolein. And the Leuchtenbergers have gotten similar toxicity results in short term experiments with mouse kidney culture and a fungus culture — both subjected to cigarette smoke, gas phase and acrolein.

To further look at effects of depriving cells of oxygen, Dr. David White, a biochemist with the University of Kentucky Medical Center, is developing a bioassay system based on measurement of components of the electron transport system (triggered by oxidation) of a bacteria in which a multiple enzyme electron transport system can be artificially created. He plans to subject the bacteria to various tobacco smoke components. Previous work by Dr. White examined the role of certain polynuclear hydrocarbons to discover their connection with cancers — thus it is logical that such hydrocarbons may be among the ingredients tested from cigarette smoke.

Thus theories that might some day tie cigarette smoke to lung cancer are abundant — but thus far no one has conclusively produced human-type lung cancers, or in fact any disease, with cigarette smoke.

Other Diseases, A Problem?

One common objection to efforts to produce an "improved" cigarette by some anti-tobacco people is that different ingredients may well be related to different diseases and conditions. Those of concern include some forms of heart disease, bronchitis and emphysema.

A recent Public Health Service pamphlet charges that

"improved" cigarette search?

each of its research institutes for fiscal 1967. One figure referred to all studies that were at least 30 per cent related to smoking and health. The other included full budgets for all projects that even touched on the subject. As a result two greatly different estimates emerged for National Heart Institute: $7.4 million when the total funding figure is used; $400,000 when the stricter formula is used.

Working with the stricter formula (although still including studies that were less than totally related to smoking and health under the 30 per cent formula) it appears HEW pumped $400,000 into NHI; $770,000 into National Cancer Institute; and $5,000 into the Environmental Health Sciences Center in North Carolina, which has now been made an Institute by National Institutes of Health.

A spokesman for HEW indicates that when the Surgeon General's office was broken up last year as a result of restructuring in HEW, the dual-breakdown method of figuring funding was abandoned. However he adds that since the HEW budget in this area has not changed, expenditures in fiscal 1968 were no doubt similar to those in fiscal 1967 given above.

There has been one significant addition to HEW expenditures this year — the Tobacco Work Group's $1.4 million, which is being appropriated through the National Cancer Institute.

USDA Funds

The largest tobacco and health research project located in one area is the $1.4 million University of Kentucky project, which is funded through the Agricultural Research Service of the U. S. Department of Agriculture, although it is also receiving some outside funding. The USDA also is sponsoring much smoking and health research at Eastern Utilization Laboratory in Beltsville, Md.

U.S. GOVERNMENT — $5.7 million

USDA	$3.07 million
HEW	2.58 million

Tobacco Reporter's canvass of various private organizations and institutes last year revealed that only two were making sizeable contributions to the smoking and health research effort: American Cancer Society and American Heart Association.

The ACS has boosted its expenditures for research from $344,000 in fiscal 1967 to $606,999 in fiscal 1968. The major effort sponsored by ACS continues to be research of Dr. Cuyler Hammond, who reportedly has observed a malignancy in the lungs of one of his smoking dogs, but will not report on this until fall because of some question over the identity of the tumor. The increase in expenditures by ACS this year, according to a spokesman for the organization, is a result of new funds for Dr. Ernest Wynder's efforts at Sloan-Kettering toward finding a "less hazardous" cigarette, and added research in the areas of behavior (why people smoke) and addiction (the role of nicotine).

(The spokesman adds that in the area of research and education — to produce the anti-smoking cigarette spots for television, for example — ACS spent $582,557 in the fiscal year through August, 1968.)

The American Heart Association, which must do a computer check of its various units to derive an exact figure for such expenditures, estimates that its funding in smoking and health research has probably increased slightly since the last such check was done for fiscal 1966. In that year AHA spent $52,000 for this research.

ORGANIZATIONS — $767,000

ACS	$607,000
AHA	60,000
Other	100,000

Additionally, smoking and health research is underway around the world. In fact, many of the most significant contributions in this area have come from industry and government sponsored research in Britain, Germany and Switzerland.

the cause of emphysema is still not known. Nevertheless, a number of theories exist on how cigarette smoking might be related to this problem of collapsed alveola — the tiny sacs in the lung. One theory might attribute this to enzymatic interference, much like that observed by Dr. Burk in cell cultures exposed to cigarette smoke.

Dr. A. C. Hilding of St. Luke's Hospital, Duluth, Minn., theorizes that failure of the muco-ciliary mechanism may be one cause of emphysema. He suggests that thickening of the mucus — which might be induced by certain irritants such as those in cigarette smoke — could strain the small air sacs. Other theories on causation of emphysema include action of certain irritants in cigarette smoke such as the aldehydes including formaldehyde that may alter the surface structure of surfactants — which protect viscosity of the mucus layer of the lung, and action of the cigarette smoke to irritate tissue to produce a cough — which may further weaken the delicate tissues of the alveoli. If these proved true, selective filters to correct the problem would not be difficult.

A number of studies might explain a tie between various lung diseases and cigarette smoke. One example is work of Dr. Gareth M. Green, who explained in the New England Journal of Medicine that cigarette smoke inhibited alveolar macrophages of rabbits — indicating that it could work against efforts of the macrophages in clearing lungs. Smoke filtered through charcoal had much less effect on the macrophages, later work of Dr. Green showed. (Alveolar macrophage and cilia are the two main forms of lung clearance.)

Interestingly, some on-going work in Switzerland seems to show that cigarette smoke tends to increase production of macrophages in animals — which could possibly offset effects of macrophage damage and inhibition that the cigarette smoke might cause.

Smoking and heart problems

Statistics do not indicate a causal relationship between cigarette smoking and heart disease, but do indicate that perhaps smoking is a contributing factor to some heart problems. Several theories have been proposed to explain this link. One holds that nicotine may induce catecholamines, which enhance aggregates of platelets in the blood and may relate to blood coagulation, and therefore thrombosis. It has also been suggested that perhaps ingredients such as carbon monoxide or hydrogen cyanide in the gas phase of smoke may act to deprive heart of oxygen through production of carboxyhemoglobin or higher serum cyanide levels. Another suggestion is that the heart may be strained in trying to pump oxygen through alveolar walls that may be thickened by reactions to cigarette smoke, or strain on the heart by effects of emphysema. All of these are theories, but if any should be proved true an "improved" cigarette could be developed.

Thus it might appear that many of those ingredients under suspicion for relating to lung cancer, might also be involved with other diseases — indicating that if cigarette smoke is causing these problems, and the mechanism can be discovered, corrective measures can probably be taken.

On page 22 is a look at cigarette smoke, its ingredients, and how they can be removed.

Exploring cigarette smoke (taking things out)

Cigarette smoke is a whirling mass of particles that form an aerosol in a complicated gas mixture. More than 1200 ingredients have already been identified in cigarette smoke — and more may be discovered.

For reference, smoke can be broken down into particulate phase and gas phase, but actually most of the components can exist in either phase. Materials vaporized in pyrolysis may remain vapors or contact a particle, where they may re-solidify, for example.

Chemical make-up of cigarette smoke as it emerges from the butt or filter end of a cigarette is quite different from the chemical make-up of the original tobacco. Even before it reaches the mouth of a smoker, chemical nature of the smoke changes. Burning causes decomposition, in which organic material in the tobacco is divided into smaller molecules. This is pyrolysis. Some of these molecules recombine to form new materials. Others such as nicotine are distilled to some extent, which is why there is less nicotine in cigarette smoke than in tobacco.

Frequently the smoke moves through a cigarette filter, where it is further altered. Perhaps the amount of particulate is reduced with a cellulose acetate filter; or some gas phase components are adsorbed by a charcoal filter. Some say a filter is more apt to pick up large and small particles, than middle-sized ones—thus even the particle sizes may be changed.

From there nature of the smoke is further changed as it enters the moist mouth, where some of the ingredients are retained, and on down into the winding passages of the lung where it must either permeate or react with the moist mucus covering — if it is to contact the lung surface. At this point the nature of the material has changed dramatically from the original tobacco.

Thus, any search for a hazardous ingredient — if indeed any exists — in tobacco smoke is not simple. A hazardous component such as residue from DDT in the tobacco might be completely distilled during combustion, for example; while an innocent nitrogen atom might combine with two oxygen atoms following pyrolysis, and later react with moisture in the lung to form nitric acid. These are both hypothetical; it is not known whether either might happen in actual smoking.

Thus far no one has conclusively produced a human-type lung cancer or other disease in laboratory animals with cigarette smoke. But there are a number of theories on how this might be done; and a number of tests have demonstrated biological *changes* can be caused at certain stages in tissue cultures and animals by several ingredients in tobacco smoke.

Here is a look at some of these ingredients, the theories that surround them and how methods might be developed to remove them if the theories proved true.

GAS PHASE

Dr. Kurt Grob of the Institute of Organic Chemistry in Zurich, Switzerland, has developed a new method of glass capillary gas chromatography for analysis of gas phase by which he has already separated about 400 components from gas phase and identified half of them. It appears gas phase is coming under close scrutiny now in Europe, and to some degree in the U. S.

Dr. Ernest Wynder, Sloan Kettering Institute, author of *Tobacco and Tobacco Smoke,* told *Tobacco Reporter* he felt it extremely unlikely that there is anything carcinogenic in gas phase. Nonetheless, a number of gas phase ingredients have been identified as irritants, many have been found ciliastatic (they destroy the cilia that clear the lung) in tissue cultures and with certain animals, while others might be possible precursors to more undesirable ingredients.

ACROLEIN — is perhaps the most toxic ciliastat in cigarette smoke, although researchers at Eastman laboratories removed acrolein from gas phase in one study and found little change in effect of the smoke in impairing cilia movement in clams. Acrolein is also an irritant. More recently Dr. Cecile Leuchtenberger used acrolein from gas phase in a short term study and found it almost as destructive as total gas phase and whole smoke on several cultures including cells from mouse kidneys.

An interesting French paper from *Comptes Rendes* in December, 1967, from notes by Camille Izard showed S.E.I.T.A. researchers have not only found both gas phase and acrolein ciliastatic, but that acrolein rendered cells of algae — *dunaliella bioculata* — susceptible to mutation.

Although ordinary impact filters such as cellulose acetate and paper remove little acrolein, Eastman Kodak Company has developed a method of adding of hexahydrotriazines that make acrolein chemically inert. At the same time silica gel filters have been developed that can act as molecular sieves for acrolein; in fact, American Filtrona's researchers have even developed a bonded one. A problem with molecular sieves is that they tend to remove only certain families of gases, and also seem to pick up water first.

Perhaps the most effective means of removing acrolein is with activated, treated charcoal which can be designed to take out 100 per cent of acrolein, although existing activated charcoal filter brands on sale in the U. S. and abroad seem to remove about 50 per cent.

ACETALDEHYDE in gas phase has irritation effects similar, although possibly less potent, than acrolein. Charcoal can also be specially treated to remove 100 per cent of this ingredient, although existing charcoal filters appear to remove less than half.

HYDROGEN CYANIDE appears to be one of the least desirable gasses in cigarette smoke. It's an irritant. Eastman researchers, after blocking out acrolein, found that HCN accounted for most of the ciliastatic effects of gas phase on clam cilia. Also, HCN could well be a primary villain if theories such as oxygen transport damage (see page 20) were to prove out in regard to smoke and humans. There is also some speculation that HCN might impair myocardial cellular respiration — possibly relating it to onset of certain heart problems.

Filters can be designed to remove HCN. Untreated activated charcoal removes about 65 per cent of this ingredient, but treated filters can be designed to take out up to 90 per cent without reducing over-all gas filtration abilities of the charcoal by more than 15 per cent. Charcoal in Lark is apparently treated to remove up to 75 per cent of the HCN and hydrogen sulfide.

It is also possible to treat cellulose acetate and paper filters for some HCN removal, while it appears an untreated cellulose acetate filter will remove about 10 per cent of HCN. Eastman has a number of patents for inorganic salt additives such as sodium phosphite that will neutralize much of the HCN. While Brown & Williamson has patented addition of certain zinc compounds to cellulose acetate that are said to reduce HCN up to 72 per cent.

Also, it appears that genetic and cultural control of the tobacco crop could be set up to reduce HCN, as the chemical is apparently formed from pyrolysis of amino acids. Drs. John M. Patterson and Walter T. Smith, Jr., organic chemists at the

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University of Kentucky research project, have discovered that production of HCN is affected by both the structure of amino acid being pyrolyzed and by the temperature of pyrolysis. They say it may be possible to control HCN by suitable selection of tobacco components and burning conditions.

CARBON MONOXIDE may act to deprive heart muscles of adequate oxygen, some theorize. It is also possible that CO could be related to any possible link between viruses and cancer; and it might act as a cellular respiratory poison under the Warburg theory, although results of Dr. Burk at NCI tend to disprove this. (See page 20.)

Although the visible effects of CO are not as clear as those of many other gasses in cigarette smoke, its relative abundance in the smoke coupled with potential role in a number of heart disease and carcinogenesis theories might someday make removal of CO necessary.

Unfortunately, CO is the one gas that can not be removed with treated activated charcoal. Ordinary cellulose acetate filters also have little effect on it. Apparently the compound could be turned into harmless carbon dioxide through oxidation, but this could well have side effects on numerous other chemicals in the smoke.

Drs. Patterson and Smith at University of Kentucky have discovered that amino acids can give rise to carbon monoxide as the result of decomposition reaction rather than from incomplete combustion—which might indicate CO content could be controlled by modifying amino acids through breeding or processing or changing burning temperatures. Also, it is apparently possible to treat tobacco to reduce CO dramatically, although side effects of the treatment on other compounds and taste are not known.

John W. Berhman, a New York City inventor, has come up with a process that reportedly reduces CO from 3.68 per cent of the smoke to about 0.63 per cent — according to tests of a private laboratory. Reportedly a cigarette company has tested the treatment.

OXIDES OF NITROGEN — Although nitrogen oxide (NO) is a mild irritant, major fears with this chemical are that it might form N-nitrosamines (a powerful but extremely volatile carcinogen that recent tests have more or less proved shows up in stored tobacco "tar" as an artifact of storage and does not occur in fresh cigarette smoke) or that it could be oxidized into NO_2 which might react with moisture to form nitric acid.

These molecules are among the smallest in cigarette smoke, and among the hardest to filter out. Although standard cellulose acetate filters do little to filter oxides of nitrogen, treatments have been developed to neutralize them. Eastman holds a patent covering addition of chlorous acid for this purpose, although this process tends to give cigarettes an odor of chlorine during prolonged storage. The company also holds patent on a process that can oxidize 95 per cent of the NO and NO_2 to harmless NO_3.

Activated charcoal filters can now be designed to remove up to 50 per cent of NO and a greater percentage of NO_2.

And Imperial Tobacco has developed a process of adding granules with a complicated formula [manganese (IV) oxide dihydroxide — $MnO(OH)_2$] that are said to reduce the oxides of nitrogen by 60 per cent.

PARTICULATE

The term "tar" generally refers to the total particulate matter (TPM) as it collects on an absolute Cambridge Filter, minus both water and nicotine.

Most of the carcinogenic ingredients identified in tobacco smoke are in the "tar," although there is some disagreement among researchers about exactly where in the "tar" they occur. (Although most agree that the total level is well below that needed to produce cancer by inhalation in humans.)

When TPM is divided, most of the carcinogenic effects can be attributed to a sub-fraction of the neutral portion that contains the polycyclic aromatic hydrocarbons, according to Drs. Ernest Wynder and Dietrich Hoffmann in *Tobacco and Tobacco Smoke.*

Apparently 3,4 benzpyrene and chrysene are among the nine carcinogenic "polycyclics" that have been identified. All of the "polycyclics" that are carcinogenic to mice have between 4 and 6 rings, although many of this type of "polycyclics" do not appear to produce cancer in animals.

A number of theories have been advanced as to why these compounds might produce cancer in laboratory tests with animals. One theory holds that the complex molecular structure of some of these compounds might be similar to the genetic molds that shape chromosomes. An oversimplified explanation of the theory might be that when the RNA transmits the genetic code to the DNA, certain complex hydrocarbons can interfere to garble the message.

At the same time, not all researchers agree the "polycyclics" account for the major carcinogenic effects of "tar." Dr. J. H. Whitehead at Harrogate Laboratory of the Tobacco Research Council in Britain has fractionated the water-insoluble material from "tar" and further divided this into polycyclic and non-polycyclic fractions. He discovered that the non-polycyclic portion demonstrated higher cancer-causing activity than the polycyclics. Thus he apparently feels the polycyclics are not major initiators of cancer while N-heterocyclic hydrocarbons in the non-polycyclic fraction may be significant. Most prevalent of the N-heterocyclics in tobacco smoke is apparently dibenz (a,j) acridine.

Studies by Wynder and Hoffmann indicate "there is no significant tumor promoting activity of dibenz (a,j) acridine, despite its strong hyperplastic effect."

To further complicate the problem of locating the carcinogenic ingredients in "tar," the sum of carcinogenic effects of all the various fractions is not as great as that of fresh TPM. Dr. F. G. Bock, Roswell Park Memorial Institute, feels this is due to imperfections in laboratory techniques. Some feel this could also be due to co-carcinogenic ingredients that occur in different fractions of the TPM.

At Chester Beaty Research Institute in Britain, Dr. F. C. Roe added 3,4 benzpyrene to the neutral fraction to see if effects were synergistic. He found that effects were merely additive.

In other stduies where 3,4 benzpyrene was added to total TPM the carcinogenicity of the material did not change in mouseback paintings. For this reason many researchers seem to feel that measurement of 3,4 benzpyrene is more a clue to identification of the polycyclic portion of ingredients rather than a cause of major carcinogenic effects of TPM.

Most significantly, neither the total carcinogenic effect of all the portions of the TPM, nor the effect produced with fresh whole TPM appear to be even close to levels necessary to induce lung cancer in humans. In fact, tobacco "tar" is a very weak carcinogen, although it appears more efficient as a tumor promoter.

Of special interest in tobacco particulate are nicotine, the "polycyclics" and "heterocyclics." Also of possible importance could be some of the ingredients in tobacco leaf that could be precursors of these ingredients.

TAR — is generally reduced non-selectively by filters. That is, most filters remove proportionate amounts of all ingredients in the TPM. There are a few exceptions. Currently experiments are underway involving treatment of tobacco, for example to change burning temperatures, in an

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effort to alter make-up of the TPM. Since the complex molecules of the "polycyclics" are formed from incomplete combustion, researchers apparently reason that these compounds might be broken up and distilled at higher temperatures, or perhaps not even formed in pyrolysis if temperatures could be lowered significantly. Interestingly, smoke from cigars, which burn at a lower temperature than cigarettes, produces more "polycyclics." Other efforts to reduce "tar" or change its composition are underway in the areas of genetics, breeding and tobacco processing.

3,4 BENZPYRENE AND "POLYCYCLICS" can reportedly be reduced by addition of Chemsol, a controversial chemical produced by High-Tor Foundation that reportedly does not affect total "tar." Apparently the chemical affects burning temperature, although side effects of the material are not known. And Herbert A. Lebert, an inventor, has now marketed a metal ring to wrinkle cigarette paper while compacting the tobacco slightly. Reasoning apparently is that this will cool the burning temperature of the cigarette.

Dr. J. W. Flesher at University of Kentucky is exploring effects of phenanthrene — an anti-carcinogen — on benzpyrene. "Polycyclics" can also apparently be affected by tobacco breeding — for example changing structure of amino acids and other possible precursors.

PHENOLS AND POLYPHENOLS are thought to be possible precursors of 3,4 benzpyrene and other "polycyclics," while polyphenols in tobacco are thought to give rise to phenols in the smoke. Some suspect phenols of being co-carcinogenic. At the same time, studies by Drs. R. Rylander and T. Dahlham have indicated that phenols are ciliastatic in chronic studies with live cats. They are also irritants. Recently Dr. Dahlham received a patent on tobacco treatment with certain oxadiazone compounds that allow cilia to remain active during smoking. It is assigned to Lorillard Corp.

Since phenols are middle molecular weight compounds they exist in both particulate and gas phases. Many commercial cellulose acetate filters include a plasticizer first used by Kent, a form of triacetin, that removes much of the phenol. This is one of the few selective filtration efforts directed toward particulate matter.

Phenols can also be removed with activated charcoal, and Eastman has developed an additive that can be used on polyolefin filters — which don't use plasticizers — to reduce phenols.

Japan Monopoly is studying lignon in processed tobacco sheet to see if it relates to increased phenols.

While University of Kentucky research has indicated that "polyphenols in tobacco leaf can be lowered by genetic control." Meanwhile, other studies have demonstrated that content of phenols in cigarette smoke may be directly related to intake by the tobacco plant of nitrogen from the soil and formation of sugars in the plant. Thus changes in fertilization might affect phenols.

AMINO ACIDS when pyrolized can form phenol, cresols, hydrogen cyanide, nitriles, fluorene, pyrene, benzflourene, methylpyrene, chrysene and benz (a) anthracene. (The last two have been identified as carcinogenic "polycyclics.") Drs. Patterson and Smith point out that there is a possibility that composition of "tar" can be modified by changing the structure of the amino acid being pyrolyzed. This might be done either through genetic changes or processing, for example proper selection of an amino acid to be used as a modifier in tobacco.

ALKALOIDS; NICOTINE AND NOR-NICOTINE — Nor-nicotine is the most prevalent secondary amine in tobacco. Major interest in secondary amines centers around theory that they might produce N-nitrosamines, which are now generally believed not to occur in fresh cigarette smoke. A National Institutes of Health project in Texas is currently re-checking this hypothesis. (However, Dr. H. Druckery at the Forschugnstelle in Hamburg, W. Germany, has produced cancer in mice with N-nitrosamines. They are so volatile the mice got cancers on their noses instead of their backs.)

Nicotine has been implicated in several heart disease theories although generally discounted as a major contributing factor by Surgeon General's Report. It can be reduced through various methods. These include everything from selection of lower nicotine tobacco (most Oriental tobacco has lower nicotine content than U. S. tobacco, for example), to selective breeding for ultra-low nicotine (this has been done at University of Kentucky), to reduction of nicotine in tobacco with a solvent. In fact, nicotine can even be selectively removed with a cellulose acetate filter, if it is specially treated. An undiluted nonacid butanetriol coating for filters has been developed recently by Eastman Kodak.

Lower nicotine can also be achieved through various methods of reducing total "tar" such as using perforated cigarette paper or filter perforations; changing to a pure cellulose or paper filter; using greater amounts of stems or processed tobacco sheet, or using "puffed" tobacco. North Carolina State University recently received much publicity on a method of freeze-drying tobacco which reduced "tar" including nicotine, while use of non-tobacco leaf such as lettuce or artificial tobacco can completely eliminate nicotine. (See page 56.) The problem here is that smokers like nicotine.

Changing smoke with filters

Contrary to opinion of many people — thanks to numerous government, and at one time tobacco industry, efforts to push low "tar" and nicotine — it is not difficult to reduce nicotine and "tar." There is also little proof that such removal would be more helpful than removal of other ingredients in tobacco smoke.

The problem is that such modifications affect the taste or draw resistance, of cigarettes, making them less popular with smokers. There is little point in making a cigarette that no one will smoke.

Proof of this is the number of cigarettes currently on the market with less than 10 mg. of "tar" (in fact, the midget Marvel has less than 4 mg.). None of these are top selling cigarettes — in fact none even has 1 per cent of the market.

An additional problem is that most efforts to change nicotine and "tar" content of cigarette smoke also result in other changes, sometimes in new ingredients that have not undergone the careful scrutiny researchers have given to those in tobacco smoke over the past few decades. This is even true of a simple system such as aeration — which allows additional air to dilute smoke through various kinds of perforations in the paper or filter. The additional air, for example, could oxidize such compounds as NO, changing it to NO_2.

Today's smokers do appear to prefer "lighter" cigarettes than smokers a decade ago, and it is interesting to note that for the past four or five years nicotine and "tar" across-the-board in the various U. S. brands has continued to drop. During this same period preference of U. S. smokers for filter cigarettes — but not those with extremely low "tar" — has grown rapidly.

In fact, in the past 15 years sales of filter cigarettes in the U. S. have